

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to June 13, 2006 Office Action
Page- 5 -

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REMARKS

Claims 1-19 are pending in the application. Claim 4 has been amended to include the full name of the abbreviation "SCI." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

Attached hereto, are the 37 C.F.R. § 1.1.32 Declarations (as "Exhibit A") of the inventors which further explain the differences between the instant invention and the cited references. Consideration and entry is respectfully requested.

Claim Objections

Claim 4 is objected to for recitation of SCI. In response Applicants have amended claim 4 to recite the full terminology, i.e. "spinal cord injury." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant objection.

Claim Rejections Under 35 U.S.C. § 102

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

Applicants respectfully traverse.

Applicants invention is directed, in part, to method of increasing motility of sperm, by providing from a subject a biological sample comprising sperm and at least one cytokine; and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

{WP333289,1}

In re Application of: Brackett N. L., et al.
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Alexander et al., neither teaches nor discloses methods of increasing sperm motility. Alexander et al., discusses diagnosing of CPPS. There is no discussion or teaching that administration of anti-cytokine antibodies or agents increase sperm motility. Furthermore, treatment of sexual dysfunction by administering anti-TNF α antibodies with a patient suffering from CPPS has no bearing on treating fertility, i.e. sexual function vs. fertility. Alexander et al., neither teaches nor discloses treatment of actual semen samples with any anti-cytokine agents. In contrast, Alexander et al., discusses systemic administration of an anti-TNF- α antibody.

Applicants further discuss in detail in the 37 C.F.R. Rule 1.132 Declarations (Exhibit "A") filed herewith, that Alexander et al. neither teaches nor discloses the instant invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-6 and 8-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu *et al* (Journal of Andrology, 2002).

Applicants respectfully traverse.

Alexander has been discussed above. Alexander et al does not teach or disclose the instant invention. Furthermore Alexander discusses sexual dysfunction which is completely different to infertility and sperm mobility. There is no motivation to combine Alexander et al., with Basu et al., as each discuss different conditions and diagnosis of CPPS as discussed by Alexander would not result in a method of treatment infertility as taught by the instant invention. Further, as stated by the inventors in the 37 C.F.R. Rule 1.132 Declaration, Basu is a co-inventor and the conception of the instant application preceded the Basu publication. As such, Basu et al is not a proper reference.

{WP333289.1}

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In view of the foregoing and Applicants Declaration, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1, 2, 5-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Faber et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

Applicants respectfully traverse.

Applicants have discussed Alexander et al. Faber does not teach or disclose a method of treating sperm mobility using anti-cytokine agents. Faber discusses endometriosis-associated infertility in females. There is no teaching or disclosure in Faber that would motivate one of ordinary skill in the art to treat male infertility nor combine the teachings of Alexander with Faber. Faber does not make up for the deficiencies of Alexander et al. Neither treats male infertility. Slesarev et al., also fails to make up for the deficiencies of Alexander and Faber. Slesarev does not teach or disclose treatment of male infertility. Vaginal application of a compound that inhibits TNF α is irrelevant to treating male infertility.

The Examiner, on page 6, sets out the reasoning for the rejection based on cited references "to treat endometriosis in women...." Applicants submit that treating male infertility as taught by Applicants is not obvious in view of the cited references standing alone or taken together. Further discussion is provided by the declarations of the inventors, filed herewith.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

{WP333289;1}

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
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CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-19 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being timely filed within the shortened statutory period and, as such, Applicants believe that no fees are due. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMANTENTERFITT



Date: September 13, 2006

Nicholas A. Zachariades, Ph.D.
Reg. No. 56,712
AKERMANTENTERFITT
P.O. Box 3188
West Palm Beach, FL 33402-3188
Tel: 561-653-5000

Docket No. 7230-9

{WP333289;1}

T-425 P. 10/40 F-719
No. 0420 P. 2

5616596313

SEP-13-06 04:50PM FROM-AKERMAN CENTERFITT

SEP. 12. 2006 12:35PM

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brockett N. L., et al. Confirmation No: 6890
Application No.: 10748,637 Examiner: SCHUBERT, L. J.
Date Filed: December 10, 2003 Group: 1651
For: INCREASING SPERM MOTILITY

Correspondence Under 37 CFR 1.81(a)
I hereby certify that this correspondence is being
deposited with the Patent Office by facsimile to 571-273-0000 or with
the U.S. Postal Service as First Class mail in an envelope
addressed to Mail Stop Amendment, Correspondence for
Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on
September 12, 2006
[Signature]
Hilario A. Zacherias Rep. No. 66,212

INTERLUZ DECLARATION

Via Facsimile No. 571-273-0000

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Nancy L. Erndt, declare as follows:

1. I am one of the named inventors and am familiar with patent application No. 10748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

2. I hold a Ph.D. in Behavioral Neuroscience and an M.D. in Andrology. I am presently employed as a Research Associate Professor of Neurological Surgery and Urology, University of Miami Miller School of Medicine. I have worked in the field of reproductive

(47 USC 1811)

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RULE 132 DECLARATION
In re Application of: Bruckett N. L., et al.
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biology for 20 years. My expertise is in Andrology and male infertility, specifically infertility of men with spinal cord injury.

3. I have authored or coauthored more than 50 scientific papers.
4. I have reviewed the Office Action dated June 1, 2006 and references cited therein. I have been asked by patent counsel Zacharukides to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art.

Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the

steps of:

- n) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- o) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

5. The Examiner has rejected claims 1, 2, 3, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Banu et al. (Journal of Andrology 2002). Claims 1, 2, and 5-

(continued)

RULE 172 DECLARATION
In re Application of: Brackbill N. L. et al
Confirmation No: 6890
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19 were rejected under 35 U.S.C. §107(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Fater et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,814,735).

6. First, I will discuss the Alexander et al. (US 6,180,355 B1) references and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indications to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the peritoneal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample collected following a prostatic massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF- α , in serinal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

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No. 0420 P. 5

The Examiner wrongly interprets Alexander's teaching. I.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indications" of CPPG. In contrast to the Alexander patent, our patent does not use cytokines to diagnose a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "to edit or" clearly referred to in the Alexander patent is CPPG or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPG, but men with spinal cord injury. Our patent does not claim that CPPG causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

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SEP-13-06 04:50PM FROM-ALEXANDER CENTERF11T
SEP. 12. 2006 12:35PM

RULJ 132 DECLARATION
in re Application of: Draschett N. L., et al.
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Application No.: 10748.637
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medical field, there is no basis for assuming that treating the women will improve CPPS. Our patient provides for treating the women to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the Basu et al. reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 11, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "use of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discloses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method related to treats conditions such as CPPS by administration of anti cytokines agents orally or parentally. Our method treats an unrelated condition, low sperm motility, by the addition said cytokine agents to the seminal plasma in vitro (see above).

10748.637

8. Third, I will discuss the Faber *et al.* reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber *et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part of a reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Stearns reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (MDP) in modulating these effects, specifically the synthesis of

(continued)

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prostaglandin E2. This proinflammatory peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev et al:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of OMPD as a treatment of pre-term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge and true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United

(continued)

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In re Application of: Brackett N. L., et al.
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Application No.: 10748,617
Page - 8 -

Sworn Code, and that such willful false statements may jeopardize the validity of the application
of any patent issued hereon.

Nancy L. Brackett
Dr. Nancy L. Brackett, Ph.D. HCLD

Sept 12, 2006
Date

(by return)

T-425 P. 17/40 F-718

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SEP-13-06 04:51PM FROM-AKRYAN SENTERFIT

SEP. 12. 2006 12:36PM

No. 0420 P. 9

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EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

Examiner: SCHUBERG, L. J.

Date Filed: December 30, 2003

Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER 37 CFR 1.8(a)
I hereby certify that this correspondence is being
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Sept 13, 2006

Nicholas A. Zacharades

Reg. No. 56,712

37 C.F.R. 1.132 DECLARATIONVia Facsimile No. 571-273-8300

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Sarmistha Basu, declare as follows:

1. I am one of the named inventors and am familiar with patent application No. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

2. I hold a Ph.D. in Science (Biochemistry). I am presently employed as Program Manager at Dow Pharmaceutical Sciences, Inc., Petaluma, California for last 5 years. I have worked in the field of Biochemistry for 7 years.

3. I have authored or coauthored more than 6 scientific papers.

{WP333281;1}

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In re Application of: Brackett N. L., et al.

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4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zachariades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:

- a) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander *et al.* (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Basu *et al.* (*Journal of Andrology* 2002). Claims 1, 2, and 5-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Faber *et al.* (*Obstetrics and Gynecology* 2001) and Slesarev (US 5,834,435).

(WP333251:1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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6. First, I will discuss the Alexander *et al* (US 6,180,355 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample excreted following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander *et al*.

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to *diagnose* a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by *systemic administration* of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the medical field, there is no basis for assuming that treating the semen will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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7. Second, I will discuss the Basu *et al.* reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

8. Third, I will discuss the Faber *et al.* reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber *et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

Page - 6 -

levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm -- zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the *female reproductive tract*.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of prostaglandin E2. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev *et al*:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMPD as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-

{WP333261;1}

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In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Sarmistha Basu
Dr. Sarmistha Basu

09/13/06
Date

(WP333261.1)

SEP. 12. 2006 1:49PM

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bruckert N. L., et al. Confirmation No: 6809
 Application No.: 10748637 Examiner: SCHUBERG, L. J.
 Date Filed: December 30, 2001 Group: 1651
 For: INCREASING SPERM MOTILITY

Continuation of U.S. Pat. No. 6,184,184
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 September 12, 2006
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 Nicholas A. Zacharias

37 C.F.R. 1.132 DECLARATION

Via Registered Mail No. 571-271-8100

Mail Stop Amendment
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, VA 22313-1450

I, Charles M. Lynne, declare as follows:

I. I am one of the named inventors and am familiar with patent application No. 10748637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

(WP257280.1)

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RULE 132 DECLARATION
In re Application of: Emanuel M. L., et al.
Confirmation No: 6890
Application No: 10748.617
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T-425 P. 26/40 F-718
No. 0421 P. 3

2. I hold an MD and am board certified in Urology. I am presently employed as a Professor of Urology at the University of Miami Miller School of Medicine. I have worked in the field of Urology for 35 years.

3. I have authored or coauthored more than 70 scientific papers.

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zacharades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the

steps of:

- a) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- b) contacting the biological sample with an agent that increases or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL-1 β , and IL-6.

SEP-13-06 04:52PM FROM-AKEMAN SENTERFIT
Sep. 12 2006 1:49PM

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu et al. (*Journal of Andrology* 2002). Claims 1, 2, and 5-

rejection)

RULE 172 DECLARATION

In re Application of: Brackett M. L., et al.

Confirmation No: 6890

Application No.: 107748.637

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T-425 P. 27/40 F-719
No. 0421 P. 4

19 were rejected under 35 U.S.C. §102(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Forbes et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,334,435).

6. First, I will discuss the Alexander et al. (US 6,180,355 B1) reference and why this patent does not teach or disclose the Instant Invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discloses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytes in the expressed prostatic secretions or by rectal exam found in a urine sample excreted following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the rest of their patent. Alexander discloses the condition(s) with respect to sexual function.

Alexander discloses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The Instant Invention is not taught or disclosed by Alexander et al.

(107748.637)

SEP-13-06 04:52PM FROM-AKEMAN CENTER/ITT
Sep. 12. 2006 1:49PM

T-425 P. 28/40 F-718
No. 0421 P. 5

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effect on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to diagnose a disease. Instead, our patent states that cytokines are agents in the semen which not immediately kill sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF- α , in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

(P. 28/40)

SEP-13-06 04:52PM FROM-AKEMAN SENTERFIT
SEP. 12. 2006 1:49PM

RULE 132 DECLARATION
In re Application of: Dumack N. L., et al.
Confirmation No.: 6890
Application No.: 10748, 617
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medical field, there is no basis for assuming that treating the women will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the Basu *et al.* reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications precluded the patent application. Basu is one of our inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

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RULE 132 DECLARATION
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No. 0421 P. 7

8. Third, I will discuss the *Faber et al.* reference and why this reference does not teach or disclose the instant invention. This reference discusses the occurrence of certain cyclooxins in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

This instant invention is not taught or disclosed by *Faber et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cyclooxins in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the *Steeney* reference and why this reference does not teach or disclose the instant invention. This reference discusses the systemic effects of TNP-alpha in a variety of male and often fatal conditions as well as pre term labor and the role of a certain neuropeptide (GMDP) in modulating these effects. Specifically the synthesis of

(NIP3327821)

SEP-13-06 04:52PM FROM-AKERMAN CENTERF11T
Sep. 12. 2006 1:49PM

RULE 172 DECLARATION
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Confirmation No: 6890
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prostaglandin E2. This (probiotic curative) peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev et al.

Neither made in fertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of CRAPD as a treatment of preterm labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge and true and that all statements made on information and belief are believed to be true, and further that these statements were made with my knowledge that will not false statements and the like so made are punishable by fines or imprisonment, or both, under §1001 of Title 18 of the United

(WFO02301)

RULE 132 DECLARATION
In re Application of: Dracott N. L., et al.
Confirmation No: 6890
Application No: 107148.617
Page - 8 -

States Code, and that each willful false statements may jeopardize the validity of the application
or any patent issued thereon.

Charles M. Lyman

Dr. Charles M. Lyman

9/12/06

Date

T-425 P. 32/40 F-718
No. 0421 P. 9

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SEP-13-06 04:53PM FROM-AKERMAN SENTERFIT

SEP. 12. 2006 1:50PM

(Inclusion)

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

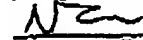
Examiner: SCHUBERG, L. J.

Date Filed: December 30, 2003

Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER 37 CFR 1.8(a)
I hereby certify that this correspondence is being
deposited either by facsimile to 571-273-8300 or with
the U.S. Postal Service as First Class mail in an envelope
addressed to Mail Stop Amendment, Commissioner for
Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on
Sep 13, 2006


Nicholas A. Zachariades, Reg. No. 58,712

37 C.F.R. 1.132 DECLARATIONVia Facsimile No. 571-273-8300

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Daniel R. Cohen, declare as follows:

1. I am one of the named inventors and am familiar with patent application No. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

2. I hold a Medical Doctor degree in Gynecology and a Medical Doctor degree in Medical Genetics. I am presently employed as Medical Director at Second Medical Opinion Services-Gracias Doctor Corporation & American Health National Network-. I have worked in

{WP333253;1}

RULE 132 DECLARATION

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the field of prenatal diagnosis of genetic diseases, cytogenetics and molecular biology (Northern Blot, Southern Blot, mitochondrial DNA sequencing, and microarray DNA technology

3. I have authored or coauthored more than 11 scientific papers, and one patent.

in Argentina (Continue cloning keratinocytes stem cell system for skin culture)

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zachariades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art.

Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:

a) providing from a subject a biological sample comprising sperm and at least one cytokine; and

b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander *et al.* (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Basu *et al.* (*Journal of Andrology* 2002). Claims 1, 2, and 5-

(WP333253:1)

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19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Faber *et al.* (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

6. First, I will discuss the Alexander *et al.* (US 6,180,355 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample excreted following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander *et al.*

{WP933253:1}

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The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to *diagnose* a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by *systemic administration* of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

(WP333253.1)

RULE 132 DECLARATION

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medical field, there is no basis for assuming that treating the semen will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

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Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokins agents to the seminal plasma in vitro (see above).

(WP333253:1)

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8. Third, I will discuss the Faber *et al.* reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in *women* caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber *et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the *female reproductive tract*.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of

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Confirmation No: 6890

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prostaglandin E2. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev *et al*:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMPD as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United

(WP333253;1)

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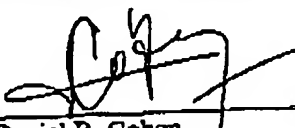
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States Code, and that such willful false statements may jeopardize the validity of the application
or any patent issued thereon.


Dr. Daniel R. Cohen

9-12-2006
Date

{WP333253:1}